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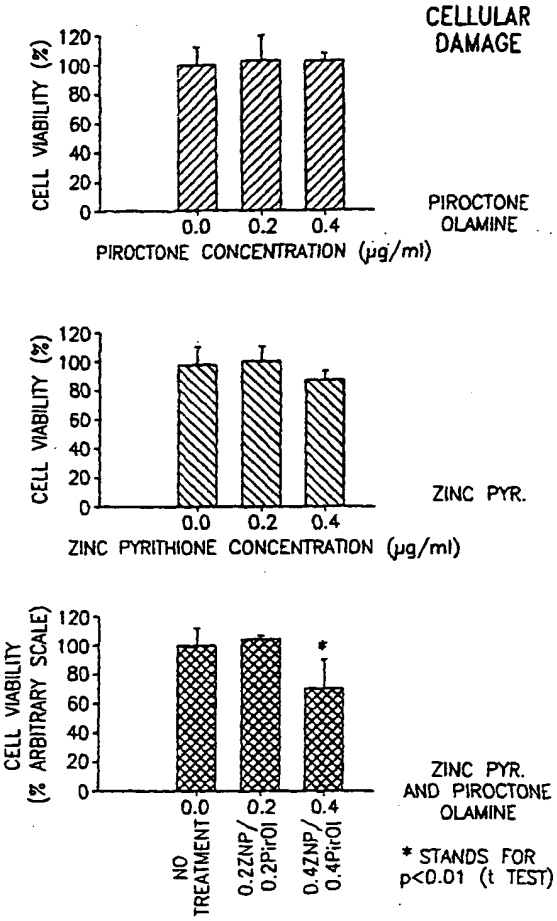
(54) Title: COMPOSITION FOR THE TREATMENT OF DANDRUFF



(57) Abstract: The present invention relates to a composition for the treatment of seborrheic dermatitis of scalp (dandruff) comprising a mixture of bisabolol, one of its derivatives or compounds comprising same with zinc pyrithione and piroctone olamine and/or their derivatives. Said composition advantageously comprises 0.001 - 20% of zinc pyrithione and 0.02 - 20% of piroctone olamine. The bisabolol is preferably part of a chamomile extract. The composition may comprise also a pharmaceutically effective compound selected for example among keratolytic agents; anti proliferatives; antifungals; antimicrobials; germicides; anti irritancy agents; anti-inflammatory agents; sterols; hair nourishment agents; lipid derivatives; refrigerants; herbal extracts; vasodilating compounds; nitric oxide donors and hair stimulating and/or hair invigorating agents. The present invention relates also to the treatment of humans and animals against seborrheic dermatitis and to a method for the treatment thereof.

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COMPOSITION FOR THE TREATMENT OF DANDRUFF

The present invention relates to a composition for the treatment of seborrheic dermatitis of the scalp (dandruff). Dandruff is a common disease involving a large amount of the population.

Organ function is totally dependent on an incessant proliferation process accompanied by a metabolic build-up and final apoptosis. The proliferation of cells is a continuous mitotic event, regulated by genetically derived forces and by environmental cellular inputs. More specifically, the cells respond to a myriad of inputs by selected biochemical transduction pathways. Therefore, a final common pathway exists in response to external hormones, cytokines, electrolytes, mechanical stimuli or specific chemicals, etc.

An imbalance of the cell multiplication process causes diseases. Especially, the skin may be affected by such imbalances, due to its unique structure and activity, which involve total cell turnover about every 50 days in the epidermis and a layer which matures without a direct vascular supply (Greaves and Shuster, eds. Springer Verlag 1989, Chapter 1, pp. 14-21). The skin multiplication rate is controlled by its unique feeding on a fibroblast layer of cells in the dermis. An imbalance of this process, i.e. an accelerated cell turnover more than the normal rate, generates in skin an incomplete cell maturation process, and results in a thick stratum corneum which causes excessive cellular shedding, known in every day life as squames. Squames may be generated by hyperproliferative diseases, such as dandruff, which implies an increase of proliferation rate of cells (x 2-3). The exact pathophysiology of rapid multiplication of cells is unknown.

Innumerous medications have been tried for the remedy of dandruff.

A general postulation in the literature claimes that a colonization by a yeast, Pityrosporum Ovale, is responsible for the disease (Shuster, Blachford, R. Soc. Med. Publ. London, 111:235-42, 1988). *Antifungals* such as ketoconazole, econazole, etc. have been used with limited success. A more recent view involves additional etiologies in the disease and suggests more therapeutic drug classes (Baran, Maibach, eds Martin Dunitz, 1994, pp 117-132). *Keratolytics* such as salicylic acid, resorcinol, alpha-hydroxy acids or selenium were used to dissolve the squames

(scales), again with limited results. Similarly, *antiproliferative* agents, such as coal tar or zinc pirythione were used for the treatment of dandruff with a temporary relief, only.

Additional approaches have been tried, such as treatment by lithium succinate. Combination therapies have been used, i.e. the treatment with a combination of e.g. a cytotoxic (zinc pyrithione or coal tar) and an antifungal; (U.S. Patent 6,075,017) a composition of fungal ergosterol biosynthesis inhibiting antifungals and a pyrithione salt (PCT WO09729733A1).

Zinc pyrithione: empirical formula: $C_{10}H_{10}N_2O_2S_2Zn$, name: bis(1-hydroxy-2(1H)-pyridinethionato) zinc or zinc, bis(2-pyridylthio)-N-oxide) and its derivatives are known as antiproliferative/cytotoxic agents, as described in USP DI Volume I, Drug Information for the Health Care Professional, DE400, (Revised: 08/13/98); and piroctone olamine, empirical formula: $C_{14}H_{23}NO_2 \cdot C_2H_7NO$, name: 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-(1H)pyridinone, 2-aminoethanol salt, or its derivatives, such as piroctone monoethanolamine, are cytotoxic, as well and were formerly used as preservatives and biocides.

It has thus been desirable to design a method and composition which can directly inhibit proliferation of the dermal layer, which is the real skin proliferation controller, to a greater extent than existing treatments. Such composition should cause the recovery of cells from their pathological hyperproliferative state and restore a normal multiplication rate. Since seborrheic dermatitis is also an inflammatory process, an additional cytotoxic agent, which possesses also anti-inflammatory attributes should be part of the composition.

It is known that bisabolol or its derivatives: Racemate, Levomenol, alpha-bisabolol, anymol, epi-form, etc. - empirical formula: $C_{15}H_{26}O$, name: (R*.R*)-.alpha.,4-dimethyl-.alpha.-(4-methyl-3-pentenyl)-3-cyclohexene-1-methanol. (synonym: 6--methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol; 1-methyl-4-(1,5-dimethyl-1-hydroxyhex-4(5)-enyl) cyclohexen-1), an active ingredient of Chamomile extract, is an anti-inflammatory, anti-irritant ingredient and a hair lighter (D. Andre et al., Int. J. Cosmet. Sci. 13:137, 1991). It has been known that the addition of bisabolol to cells does not affect their proliferation. Unexpectedly it has beend discovered that the addition of bisabolol to cytotoxic agents converts the

bisabolol into a cytotoxic agent. This has been shown by the inhibition of the fibroblast (dermal) layer in a proliferative assay. Thus, we found agents active on fibroblast layer which control proliferation and can further control immature keratinization and diminish squame generation. The final result should be regeneration of normal functioning to skin, slowing down of replication and transition to normal proliferation, which is desirable in the treatment of dandruff.

The present invention thus consists in a composition for the treatment of seborrheic dermatitis of scalp (dandruff) comprising a mixture of bisabolol, one of its derivatives or compounds comprising same with zinc pyrithione and piroctone olamine and/or their derivatives. The bisabolol may be part of a Chamomile extract.

The composition according to the present invention comprises :

1. Bisabolol (either pure or racemic) , from 0.001-25 % (all percentages are indicated herein in w/w), preferably between 0.01-10 % and advantageously between 0.05-1.0 % by weight; or a chamomile extract, from 0.001-75 %, preferably between 0.01-25 % and advantageously between 0.1-5 % by weight;
2. Zinc pyrithione in a concentration from 0.001-20.0 %, preferably between 0.1-5 % and advantageously between 0.5-2% by weight; and
3. Piroctone olamine in a concentration from 0.001-20.0 %, preferably between 0.05-5 % and advantageously between 0.2-2% by weight.

The composition according to the present invention may be topically applied as such or internally ingested within a suitable carrier, solvent, emulgent, extract, a solution e.g. water, alcohol, an oil, a suspension; microemulsions, microcapsules, vesicles, etc.

The active agents may be formulated into various compositions, e.g. a lotion, a conditioner, a hair tonic, a shampoo, a lotion with conditioner, a gel, a styling gel, a mousse, a styling wax, a mask, an aerosol, a moisturizer, a powder, a perfume, a brilliantine, a pomade, a dye, a cream, an ointment, etc.

The composition according to the present invention might be formulated, e. g. as an internally ingested tablet, capsule, drops or suspension.

The above composition can be used alone or in conjunction with a pharmaceutical effective compound selected among:

1. Keratolytic agents such as salicylic acid, sulphur, resorcinol, selenium, alpha hydroxy-carboxylic acids, etc.;
2. Anti proliferatives, e.g. coal tar, selenium, etc.;
3. Antifungals, e.g. ciclopyroxolamine, azoles (such as ketoconazole, bifonazole), metronidazole, undecylenic acid and derivatives of the said compounds, etc.;
4. Antimicrobials, e.g. aluminium chloride, chlorothymol, hexamine, zinc salycilate, zinc sulphide, triclorocarban, triclosan, etc.;
5. Germicides, such as phenols, hydroxyquinolones, undecenoic acids, etc.;
6. Anti irritancy agents, such as triterpenes, polyciclic polyenes or saponins, etc.;
7. Anti-inflammatory agents, e.g. cyclo-oxygenase inhibitors, panthenol, comilower extract, guaiazulene, etc.;
8. Sterols, e.g. medicated low (hydrocortisone), intermediate (mometasone) to high (betamethasone, dexamethasone); potency steroids, of plant origin, e.g. phytosterols such as glycyrrhizic acid and derivatives, etc.;
9. Hair nourishment agents, such as vitamins, e.g. tocopherol (Vitamin E) and its derivatives, Vitamin B6, vitamin C, biotin, pantothenic acid, Vitamin D and its derivatives; amino acids e.g. arginine, citrulline, ornithine, serine and methionine; organic acids, e.g. lactate or malate, minerals and metals, e.g. zinc and its derivatives, magnesium, aluminum, death sea minerals; eugenol, polyamines and antioxidants, etc.;
10. Lipid derivatives, e.g. mineral oil, vegetable oil, animal and synthetic oil, fatty alcohol, saturated and unsaturated fatty acids, waxes, squalene, etc.;
11. Refrigerants, e.g. menthols, camphor;
12. Herbal extracts which restore the skin natural protective factor ability, such as aloe vera, rosemary, tea tree oil or thyme, etc.;
13. Vasodilating compounds or nitric oxide donors, e.g. of natural source (arginine) or medicated (nitroprusside, sodium nitrite), etc.; and
14. Hair stimulating and /or hair invigorating agents, e.g. saw palmetto, diazoxide, glycirrhizic acid or 5 alpha reductase inhibitors, etc.

The amounts of said derivatives may be varied in accordance with the specific requirements.

The composition according to the present invention may be prepared by conventional methods, as becomes apparent from the Experiments given hereinafter.

The composition according to the present invention is suitably applied in portions of about 1 – 10 ml/daily from 1-7 times weekly, advantageously 5 ml/daily each other day.

The present invention consists also in the use of a composition according to the present invention for the treatment of humans and animals against seborrheic dermatitis.

The present invention consists also in a method for the treatment of humans and animals against seborrheic dermatitis with a composition according to the present invention.

Example 1

Fibroblast cells, the feeding layer of the skin, were exposed to the addition of bisabolol, piroctone olamine and zinc pyrithione. Bisabolol alone was not antiproliferative. Whenever bisabolol was added to cells previously treated with piroctone olamine and zinc pyrithione, the unexpected conversion of bisabolol into an antiproliferative agent was observed.

a. Methodology

Tetrazolium salt assay

The 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) colorimetric reaction is based on the uptake of tetrazolium salt exclusively by live cells and its reduction to a soluble violet (formazan) compound. The absorbance of formazan is proportional to the amount of active mitochondrial enzyme succinate-dehydrogenase of the cells and cell viability. Fibroblast 3T3 cells were seeded at 30000 cells/well in 96-well microtiter wells (Corning) and grown until confluence. The absorbance spectrum of MTT was determined by a diode array spectrophotometer (Hewlett Packard, 8452A). MTT exhibited peak absorbance at 560 nm and minimal readings beyond 620 nm, as previously shown. A microplate reader (Thermomax, Molecular Devices) was used to read absorbance at 550 nm with background subtraction at a reference absorbance of 650 nm at 25 EC (Methodology in Dascalu A, Peer A, Academic Radiology, 1:140-145, 1994).

b. Experiment

The experiments employed confluent cells which were loaded with 0.15 µg/ml of MTT and dark incubated at 37 ° C. Four hours later the media was removed by plate flipping and 100 µl of DMSO were added to each well in order to solubilize the formazan crystals. Results were expressed as compared to control values of untreated cells and each result consisted of three to six repeated measurements in at least two different experiments. Fibroblast cells were exposed to active ingredients at the indicated concentrations for about 4 hours prior to optical density readings.

c. Results

Both zinc pyrithione and piroctone olamine may cause antiproliferative and cytotoxic effects. First of all, the minimal concentration of these compounds, which does not cause a cytotoxic effect, has to be determined. Figure 1a demonstrates that addition of 0.2 µg/ml - 0.4 g µg/ml piroctone olamine doesn't cause any effects on cellular viability (a threefold concentration of 1.2 µg/ml caused a 10% decrease of cell viability, data not shown). Zinc pyrithione did not cause any cytotoxic effect at 0.2 µg/ml, but at 0.4 µg/ml a 10 % decrease of viability was observed (Fig. 1b). Therefore, we employed a concentration of 0.2 µg/ml zinc pyrithione and 0.2 µg/ml of piroctone olamine, which did not affect fibroblast viability (Fig. 1 c).

Addition of bisabolol at 1.0 % (Fig. 2) resulted in a small decrease of cellular viability which did not achieve any statistical significance [One Way Analysis of Variance, Multiple Comparison test (Student-Newman-Keuls)]. The same concentration of bisabolol was added to fibroblasts already treated with zinc pyrithione 0.2 µg/ml and piroctone olamine 0.2 µg/ml (concentrations which do not affect cell viability, as shown in Fig. 2). Surprisingly, a distinct cytotoxic effect on cells was observed (Fig. 2). It is shown that bisabolol addition decreased significantly the cell viability as compared to control untreated cells or cells treated by bisabolol solely ($p<0.05$, One Way Analysis of Variance, Multiple Comparison test of Student-Newman-Keuls).

It has thus been shown that bisabolol, a compound without a known cytotoxic effect, can reduce cellular viability of fibroblasts, provided the cells have

been treated with additional agents. In order to prove this activity, one has to use innocent low concentrations of cytotoxic agents, which by themselves do not decrease cell viability.

In order to further consolidate this unexpected finding, a dose-response curve was performed. Figure 3 demonstrates that at a concentration of 0.05% Bisabolol, no effects on cell viability can be seen. However, above this concentration, at 0.1, 0.4 and 1.0 %, an increased damage to cellular viability is observed (Figure 3, $p<0.05$).

The present invention will be illustrated by the following Examples without being restricted by them. Said Examples use composition being active in the field of dandruff treatment.

EXAMPLE II

Exemplary formula for topical formulation of a composition according to the present invention in a shampoo based formula.

Ingredient	**% by Weight**
Zinc pyrithione (48% Dispersion)	1.50
Piroctone olamine	0.60
Bisabolol	0.25
Magnesium aluminium silicate	1.20
Tetrasodium pyrophosphate	0.06
Deionized water	51.39
Sodium laureth sulfate	40.00
Myristamide DEA	5.00
Citric Acid (for pH adjustment to 6-7)	q.s.
Preservative; Color ; Fragrance	q.s.

EXAMPLE III

Exemplary formula for topical formulation of a composition according to the present invention in a creamy based formula.

Ingredient	**% by Weight**
Zinc pyrithione (48% Dispersion)	1.50
Piroctone olamine	0.75
Bisabolol	0.65
Sodium methyl cocoyl taurate	69.00
Sodium methyl oleyl taurate	14.35
Sodium cocoyl sarcosinate	3.00
Water	10.75
Citric Acid (for pH adjustment to 6 – 7)	q.s.
Preservative; Color; Fragrance	q.s.

EXAMPLE IV

Exemplary formula of a composition according to the topical formulation according to the present invention in a shampoo formula with a hair invigorating compound:

Raw Material	**% by Weight**
Zinc pyrithione (48% dispersion)	1.20
Piroctone olamine	0.60
Alpha bisabolol	0.10
D-panthenol	0.10
Magnesium aluminium silicate	1.20
Tetrasodium pyrophosphate	0.06
Deionized water	51.84
Sodium laureth sulfate	39.90
Myristamide DEA	5.00
Citric Acid (for pH adjustment to 6-7)	q.s.
Preservative; Color ; Fragrance	q.s.

Example V

Antidandruff cream-shampoo formula of a composition according to the present invention for normal and dry-hair dispensed by pump hair lotion.

INGREDIENT	% w/w	FUNCTION
Aqua	50.00	Solvent, Carrier
Sodium laureth-3 sulfate	20.00	Anionic surfactant
Disodium cocoamphodiacetate	10.00	Amphoteric surfactant
Cocamide DEA	0.50	Foam booster
Hydroxypropyl guar (and) Hydroxypropyltrimonium chloride	1.00	High conditioning Thickener
Piroctone-olamine	1.00	Active ingredient
Bisabolol	0.50	Active ingredient
Triclosan	0.50	Preservative
Zinc pyrithione 48%	2.10	Active ingredient
Perfume	0.50	Fragrance
Citric Acid	q.s.	pH-adjustment
Sodium chloride	q.s.	Thickener
Aqua	Up to 100	Solvent, Carrier

Example VI

Antidandruff lotion-shampoo formula of a composition according to the present invention for normal and dry-hair dispensed by pump hair lotion.

INGREDIENT	% w/w	FUNCTION
Part I		
PEG-5-cethet-10 phosphate (crodafos SG)	2.00	Anionic surfactant
Perfume	0.50	Fragrance
Sodium lauryl ether sulfate 28%	30.00	Anionic surfactant
Bisabolol	0.50	Active ingredient
Triclosan	0.50	Preservative
Part II		
Aqua	50.00	Solvent,vehicle
Cocoamidopropyl betaine	12.00	Amphoteric surfactant
Piroctone-olamine	1.00	Active ingredient
Part III		
Zinc pyrithione 48% dispersion	2.10	Active ingredient
Citric Acid	q.s.	pH-adjustment
Aqua	q.s. to 100	

Example VII

Antidandruff cream-shampoo formula of a composition according to the present invention for normal and oily-hair dispensed by pump hair lotion

INGREDIENT	% w/w	FUNCTION
PART I		
Acrylate/steareth 20 metacrylate copolimer	3.00	Anionic polymer, Thickener
Triethanolamine lauryl sulfate 40%	24.25	Anionic surfactant
Sodium lauroyl sarcosinate 30%	10.00	High-foaming anionic surfactant
C12-15 alkyl lactate	1.00	Foam booster, thickening agent
Piroctone-olamine	1.00	Active ingredient
Aqua	50.00	Solvent, Carrier
PART II		
Bisabolol	0.75	Active ingredient
Tocopheryl acetate	0.10	Antioxidant
Triclosan	0.50	Preservative
Zinc pyrithione 48% dispersion	2.10	Active ingredient
Perfume	0.50	Fragrance
Citric Acid	q.s.	pH-adjustment
Sodium chloride	q.s.	Thickener
Aqua	Up to 100	Solvent, Carrier

Example VIII

Antidandruff cream for scalp and hair-care mask formula of a composition according to the present invention for oily and damaged-hair, dispensed by pump hair lotion.

INGREDIENT	% w/w	FUNCTION
Part I		
Aqua	q.s. up to 100	Solvent, vehicle
Propylene glycol	2.00	Cosolvent
Part INVENTIVE IMPROVEMENT		
Isostearyl neopentanoate	4.00	Non greasy emollient
Polyquaternium – 2	1.00	Conditioner, hair protector
Isodecyl isononanoate	1.50	Non greasy emollient
Cetearyl alcohol (and) ceteareth-20	4.00	Emulgator
Cetearyl alcohol	6.00	Fatty alcohol
Lactate myristyl	1.00	Emulgator
Piroctone-olamine	1.00	Active ingredient
Part III		
Hydrolysed keratin	0.50	Hair protector
Part IV		
Bisabolol	0.50	Active ingredient
Zinc pyrithione 48% dispersion	2.10	Active ingredient
Triethanolamine 99%	q.s.	pH – controler
Propylene glycol (and) diazolidinyl urea (and) Methyl paraben (and) propyl paraben	0.3	Preservative
Perfume	0.50	Fragrance

Example IX

Antidandruff cream for scalp mask formula of a composition according to the present invention for dry and damaged-hair, dispensed by pump hair lotion.

INGREDIENT	% w/w	FUNCTION
Part I		
Glyceryl stearate (and) PEG-100 stearate	7.00	Emulsifier
Cetearyl alcohol	6.00	Fatty alcohol
Wheat(triticum vulgare)germ oil	4.00	Natural vegetal triglyceride
Coconut(cocos nucifera) oil	5.00	Natural vegetal triglyceride
Mineral oil	7.00	Emollient
Piroctone-olamine	1.00	Active ingredient
Part INVENTIVE IMPROVEMENT		
Aqua	q.s.up to 100	Solvent, vehicle
Part III		
Dimethicone (and) laureth-8 (and) succinoglycan	4.00	Hair protector
Hydroxypropyltrimonium hydrolyzed wheat protein	0.50	Conditioner
Propylene glycol (and) diazolidinyl urea (and) methyl paraben (and) propyl paraben	0.20	Preservative
Zinc pyrithione 48% dispersed	2.10	Active ingredient
Bisabolol	0.50	Active ingredient
Citric Acid 50 % solution	q.s.	pH-controler
Perfume	0.50	Fragrance

CLAIMS

1. A composition for the treatment of seborrheic dermatis of scalp (dandruff) comprising a mixture of bisabolol, one of its derivatives or compounds comprising same with zinc pyrithione and piroctone olamine and/or their derivatives;
2. A composition according to Claim 1, which comprises 0.001 - 20% of zinc pyrithione;
3. A composition according to Claim 1 or 2, which comprises 0.02 - 20% of piroctone olamine;
4. A composition according to any of Claims 1 to 3, which comprises 0.001 - 25% of bisabolol;
5. A composition according to Claim 4 wherein the bisabolol is part of a chamomile extract;
6. A composition according to any of claims 1 to 5 which comprises one or more pharmaceutical effective compounds;
7. A composition according to claim 6 whereis said pharmaceutical compound is selected among keratolytic agents; anti proliferatives; antifungals; antimicrobials; germicides; anti irritancy agents; anti-inflammatory agents; sterols; hair nourishment agents; lipid derivatives; refrigerants; herbal extracts; vasodilating compounds; nitric oxide donors and hair stimulating and/or hair invigorating agents.
8. A composition according to claims 6 or 7 wherein the keratolytic agents are selected among salicylic acid, sulphur, resorcinol, selenium and alpha hydroxy-carboxylic acid;
9. A composition according any of claims 6 to 8 wherein the anti proliferative is selected among coal tar and selenium;
10. A composition according any of claims 6 to 9 wherein the antifungal is selected among cyclopyroxolamine, azoles (e.g. ketoconazole, bifonazole), metronidazole, undecylenic acid and derivatives of the said compounds;
11. A composition according any of claims 6 to 10 wherein the antimicrobial is selected among aluminium chloride, chlorothymol, hexamine, zinc salycilate, zinc sulfide, trichlorocarban and triclosan;

12. A composition according any of claims 6 to 11 wherein the germicide is selected among phenols, hydroxyquinolones and undecenoic acids;
13. A composition according any of claims 6 to 12 whereas the irritancy agent is selected among triterpenes, polyciclic polyenes and saponins;
14. A composition according any of claims 6 to 13 whereas the anti-inflammatory agent is selected among cyclo-oxygenase inhibitors; panthenol; cumilar extract and guaiazulene.
15. A composition according any of claims 6 to 14 whereas the sterol is selected among medicated low (hydrocortisone), intermediate (mometasone) to high (betamethasone, dexamethasone) potency steroids, and potency steroids of plant origin, e.g. phytosterols such as glycyrrhizic acid and derivatives;
16. A composition according to any of claims 6 to 15 whereas the hair nourishment agent is selected among vitamins, e.g. tocopherol (Vitamin E) and its derivatives, Vitamin B6, vitamin C, biotin, pantothenic acid, Vitamin D and its derivatives; amino acids e.g. arginine, citrulline, ornithine, serine and methionine; organic acids, e.g. lactate or malate, minerals and metals, e.g. zinc and its derivatives, magnesium, aluminum, death sea minerals; eugenol, polyamines and antioxidants;
17. A composition according to any of claims 6 to 16 whereas the lipid derivative is selected among mineral oil, vegetable oil, animal and synthetic oil, fatty alcohol, saturated and unsaturated fatty acids, waxes and squalene;
18. A composition according to any of claims 6 to 17 wherein the refrigerant is selected among menthols and camphor;
19. A composition according to any of claims 6 to 18 wherein the herbal extract is selected among aloe vera, rosemary, tea tree oil and thyme;
20. A composition according to any of claims 6 to 19 wherein vasodilating compounds and nitric oxide donors are selected among natural source (arginine) or medicated (nitroprusside, sodium nitrite);
21. A composition according to any of claims 6 to 20 wherein hair stimulating and hair invigorating agents are selected among saw palmetto, diazoxide, glycirrhizic acid or 5 alpha reductase inhibitors.

22. The use of a composition according to any of claims 1 to 21 for the treatment of humans and animals against seborrheic dermatitis substantially as herein described with reference to the examples.

23. A method for the treatment of humans and animals against seborrheic dermatitis with a composition according to any of claims 1 to 21.

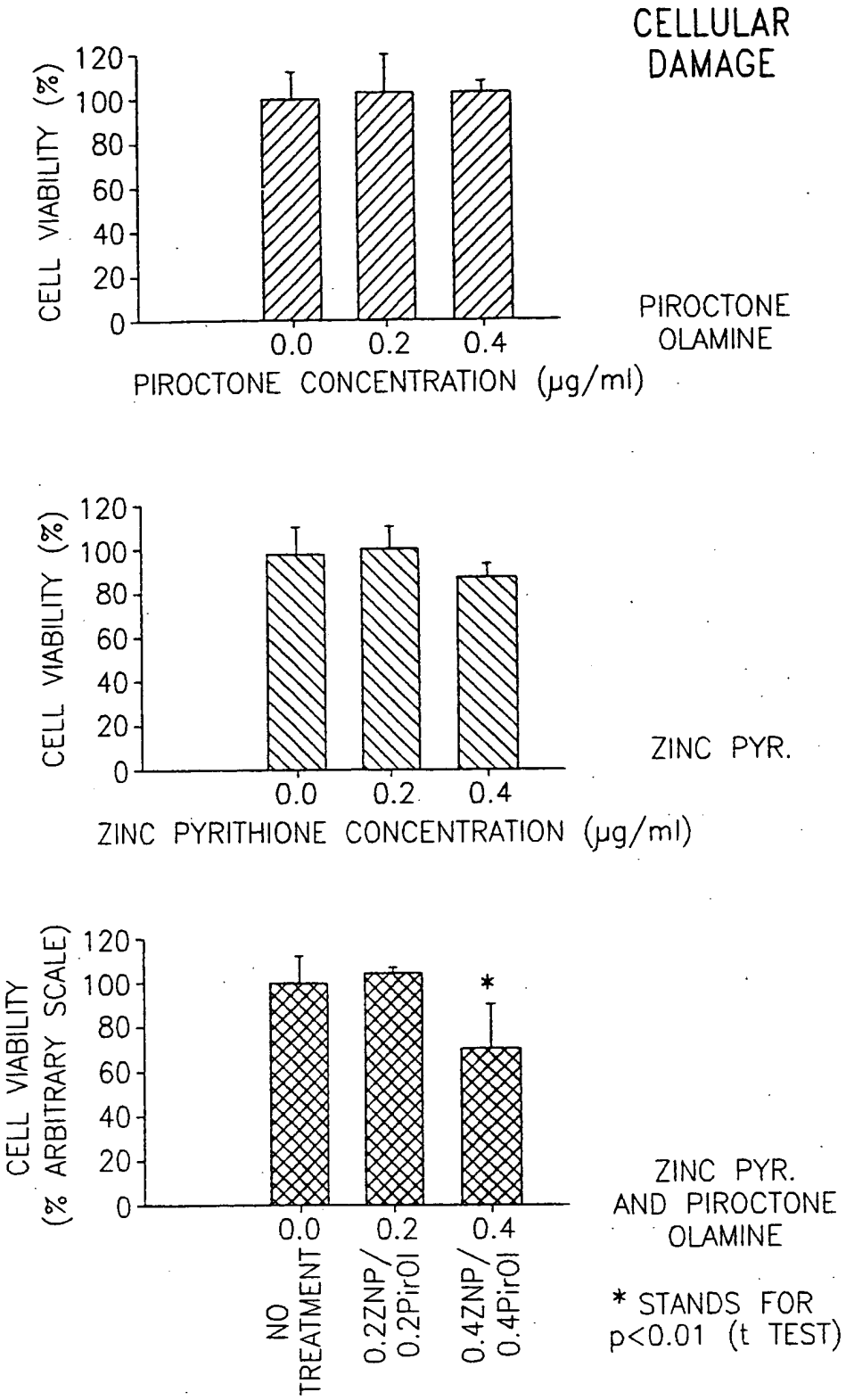
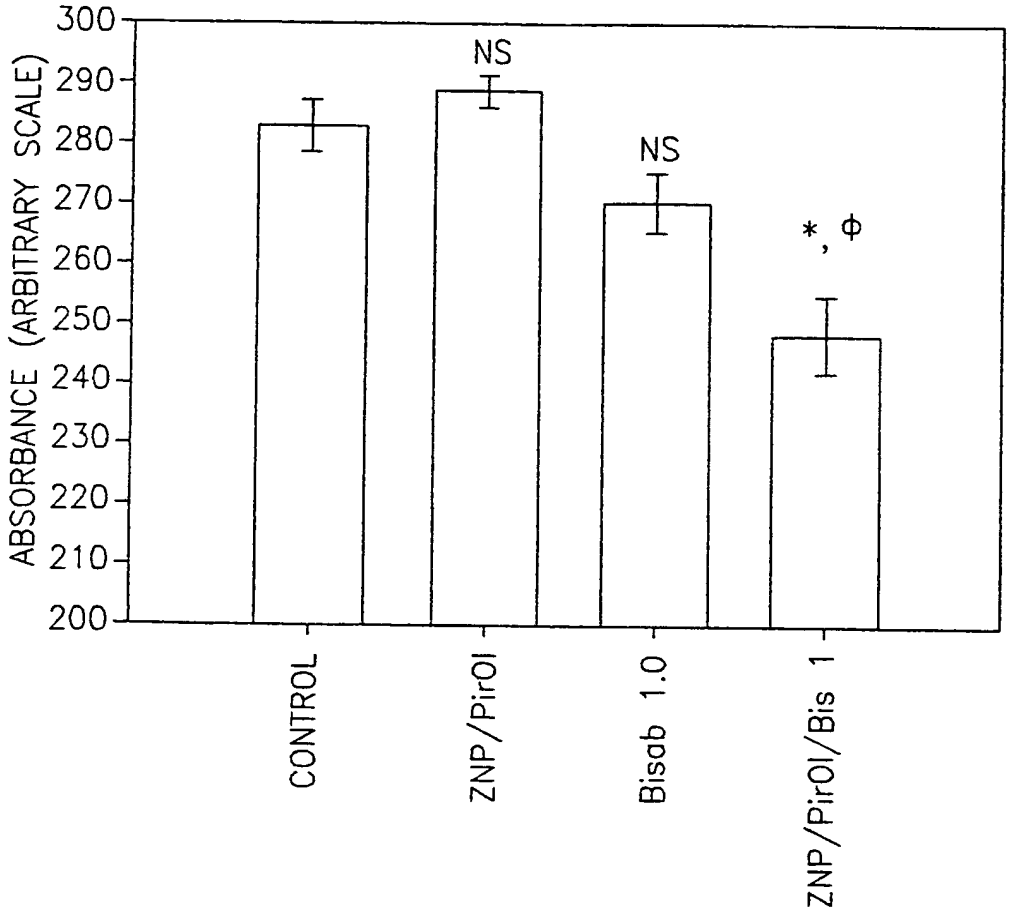

CELLULAR DAMAGE
CELL VIABILITY (%)
120
100
80
60
40
20
0
0.0
0.2
0.4
PIROCTONE CONCENTRATION (µg/ml)
PIROCTONE OLAMINE
CELL VIABILITY (%)
120
100
80
60
40
20
0
0.0
0.2
0.4
ZINC PYRITHIONE CONCENTRATION (µg/ml)
ZINC PYR.
CELL VIABILITY (% ARBITRARY SCALE)
120
100
80
60
40
20
0
*
0.0
NO TREATMENT
0.2
0.2ZNP/ 0.2PirOl
0.4
0.4ZNP/ 0.4PirOl
ZINC PYR. AND PIROCTONE OLAMINE
* STANDS FOR p<0.01 (t TEST)

FIG.1

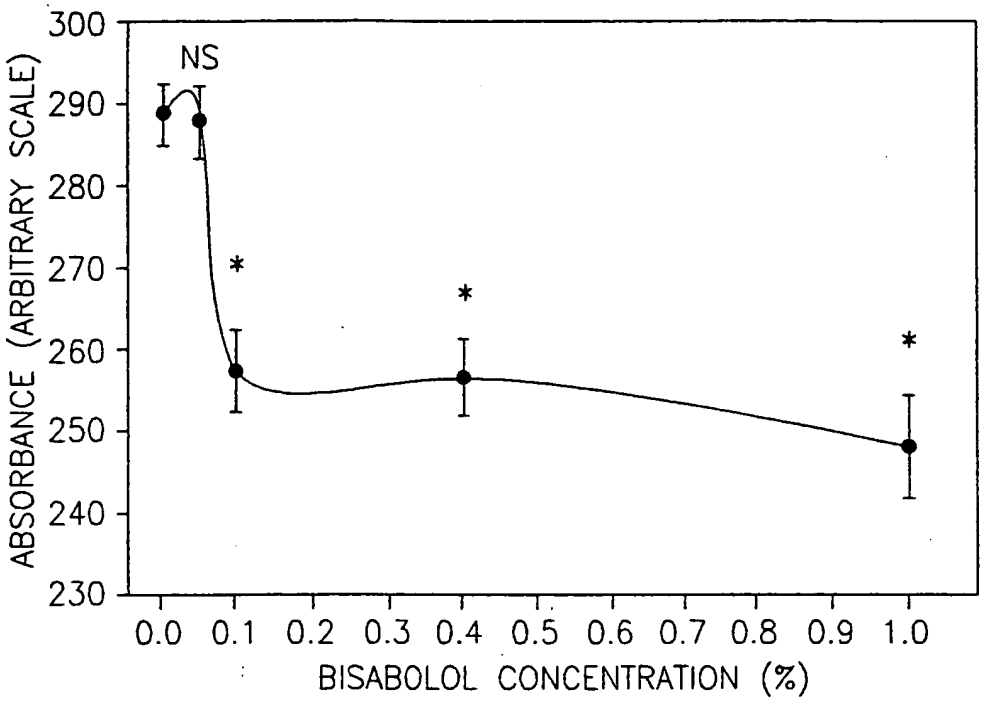


* = $p<0.05$ AS COMPARED TO BISABOLOL 1.0%

Φ = $p<0.05$ AS COMPARED TO CONTROL OR ZNP/PirOI

NS = NON SIGNIFICANT AS COMPARED TO CONTROL

FIG.2



* = $p<0.05$ AS COMPARED TO "0.00" CONCENTRATION

NS = NON SIGNIFICANT AS COMPARED TO "0.00" CONCENTRATION

FIG.3

INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/IL 00[redacted]349

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; UEDA, GOROSAKU: "Cosmetic hair preparations containing piroctone olamine and water-soluble sulfur and/or UV absorbers" retrieved from STN Database accession no. 110:160216 CA XP002164477 abstract & JP 63 179813 A (EIKODO AND CO., LTD., JAPAN) 23 July 1988 (1988-07-23) ---	1-23
Y	EP 0 158 481 A (PROCTER & GAMBLE) 16 October 1985 (1985-10-16) page 2, line 5 -page 4, line 37; examples --- -/--	1-23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

°A° document defining the general state of the art which is not considered to be of particular relevance

°E° earlier document but published on or after the international filing date

°L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

°O° document referring to an oral disclosure, use, exhibition or other means

°P° document published prior to the international filing date but later than the priority date claimed

°T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

°X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

°Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

°&° document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2001	18/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Simon, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IL 00 [redacted] 49

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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,A	WO 98 50005 A (MEDLOGIC GLOBAL CORP) 12 November 1998 (1998-11-12) page 56 -page 107	1-23
A	DE 41 33 085 A (MENGOLI FRANCO) 1 April 1993 (1993-04-01) column 3, line 32 - line 39; claim 2	1-23
A	FR 2 741 265 A (FABRE PIERRE DERMO COSMETIQUE) 23 May 1997 (1997-05-23) page 4, line 19 - line 33	1-23

INTERNATIONAL SEARCH REPORT

Information [redacted] patent family members

Intern [redacted]nal Application No
PCT/IL 0[redacted]849

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FR 2741265 A	23-05-1997	EP 0866715 A	30-09-1998
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